Thermolysis of 2-diazo-3-aryl ketoesters: New route to α-aryl malonates and aromatic esters

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Thermolysis of 2-diazo-3-aryl ketoesters: new route to α-aryl malonates and aromatic esters

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ABSTRACT

Thermochemical excitation enabled efficient α-aryl malonates synthesis from 2-diazo-3-aryl ketoesters and alcohols under transition metal-free reaction conditions. Furthermore, an unusual C–C bond cleavage and C–O/(N) bond formation occurred when MeOH/(RNH_2) was used as the nucleophile, furnishing corresponding aromatic esters/(amides) in high yields.

1. Introduction

Substituted phenylacetic acids and their derivatives are valuable structural motifs in natural products[1] and pharmaceuticals,[2] as found in nonsteroidal anti-inflammatory drugs (e.g., indometacin, sulindac, diclofenac).[2c] Beyond that, phenylacetic acids and derivatives showed good directing ability in palladium-catalyzed C–H functionalization for organic synthesis by Yu group in recent years.[3] Among them, α-aryl malonates have their own special potential in the synthesis of α-aryl acids and others.[4] Therefore, there is a continued demand for efficient syntheses of these compounds. In recent years, transition metal-catalyzed cross-coupling has become an important strategy to add various functional groups to aryl halides. For instance, enolates have been utilized for palladium-catalyzed α-arylation to furnish α-aryl carbonyl compounds (Figure 1a),[5] such as α-aryl ketones,[6] amides[7] and esters.[8] Beyond that, a significant advance to access these molecules has been accomplished with copper complexes through direct arylation of aryl iodide/bromide and 1,3-dicarbonyl derivatives,[9] including the first enantioselective Ullmann-Hurtley condensation, which was developed by Ma and co-workers in 2006.[10]

On the other hand, diazo compounds, due to its high reactivity, have recently attracted considerable attention in transition-metal catalysis.[11] However, a more classic conversion of α-diazo ketones into α-aryl carbonyl derivatives has been developed over 100 years. Since the first report on the Wolff rearrangement in 1902,[12] it has been widely employed as a powerful tool for the preparation of carboxylic acid homologues[13] and the formation of strained cyclic systems.[14] Generally, the early Wolff rearrangements were induced via thermolysis[12, 14b] and silver(I) catalysis [15, 14b] thus yielding a ketene as an intermediate, which underwent nucleophilic attack to generate carboxylic acid derivatives (Figure 1b).[13, 14]

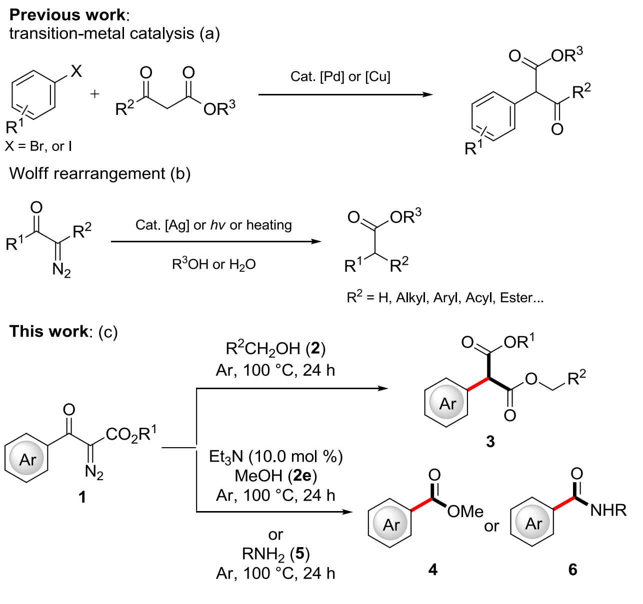

Figure 1. Syntheses of α-aryl carbonyl compounds.

Thereafter, Süs[16] as well as de Jonge[17] pioneered photolysis to be an efficient procedure for the Wolff rearrangement. In 1951, Horner/Spietschka subsequently reported that methyl 2-diazo-3-

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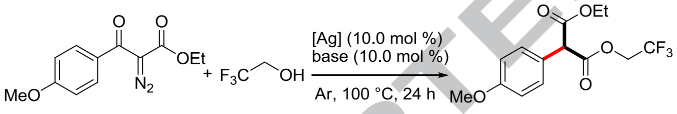
oxo-3-phenylpropanoate can be excited by *uv* light in methanol or H_2O to form α-aryl carbonyl derivatives.[18, 13c] Despite these major advances, we became intrigued by developing a specific method for selective synthesis of unsymmetrical α-aryl malonates by Wolff rearrangement. Thus, we herein describe a metal-free convenient and highly efficient protocol for the synthesis of diverse α-aryl malonates excited by thermolysis and an unusual nucleophilic addition/elimination to deliver corresponding aromatic esters/amides using 2-diazo-3-aryl-3-oxopropanoates as starting materials (Figure 1c).

Generally, Wolff rearrangement is sensitive to the Ag(I) catalysts in the presence of alkaline reagents.[14a] Thus, we initiated our studies by testing the feasibility of the envisioned catalytic system, consisted of $AgSbF_6$ and Et_3N, catalyzed decomposition of ethyl 2-diazo-3-(4-methoxyphenyl)-3-oxopropanoate (**1a**), along with 2,2,2-trifluoroethanol (**2a**) as the nucleophile and reaction medium. Fortunately, the desired rearrangement product 3aa was obtained in excellent yield (Table 1, entry 1). However, omission of Et_3N or decreasing reaction temperature resulted in a significantly negative effect (entries 2–3). Among a set of representative silver(I) sources, $AgSbF_6$ was identified to be the ideal choice (entries 1, 4–8). To our surprise, the desired product **3aa** was delivered in the same high yield in the absence of $AgSbF_6$ (entry 9), as was also observed when only employing catalytic amount of DBU as the alkaline reagents, albeit in a slightly reduced yield (entry 10). These results indicated the reaction was excited by thermolysis, rather than silver(I) catalysis. Indeed, the reaction, by only heating, gave **3aa** in 79% yield (entry 11). However, stoichiometric TFE failed to generate the rearrangement product when toluene or 1,4-dioxane as the reaction medium, which indicated solvent amount of alcohol is required for the reaction (entries 12–13).

Table 1. Synthesis of α-aryl malonate through thermolysis of 2-diazo-3-aryl ketoester **1a**.[a]



1a **2a** **3aa**

Entry	[Ag]	base	Yield (%)[b]
1	**$AgSbF_6$**	**Et_3N**	**83**
2	$AgSbF_6$	--	trace
3	$AgSbF_6$	Et_3N (50 ℃)	9
4	$AgSbF_6$	Et_3N	62
5	AgOAc	Et_3N	51
6	AgOTf	Et_3N	76
7	$AgBF_4$	Et_3N	69
8	$AgPF_6$	Et_3N	70
9	--	**Et_3N**	**83**
10	--	DBU	73
11	--	--	**79**
12	--	--	<5[c]
13	--	--	0[d]

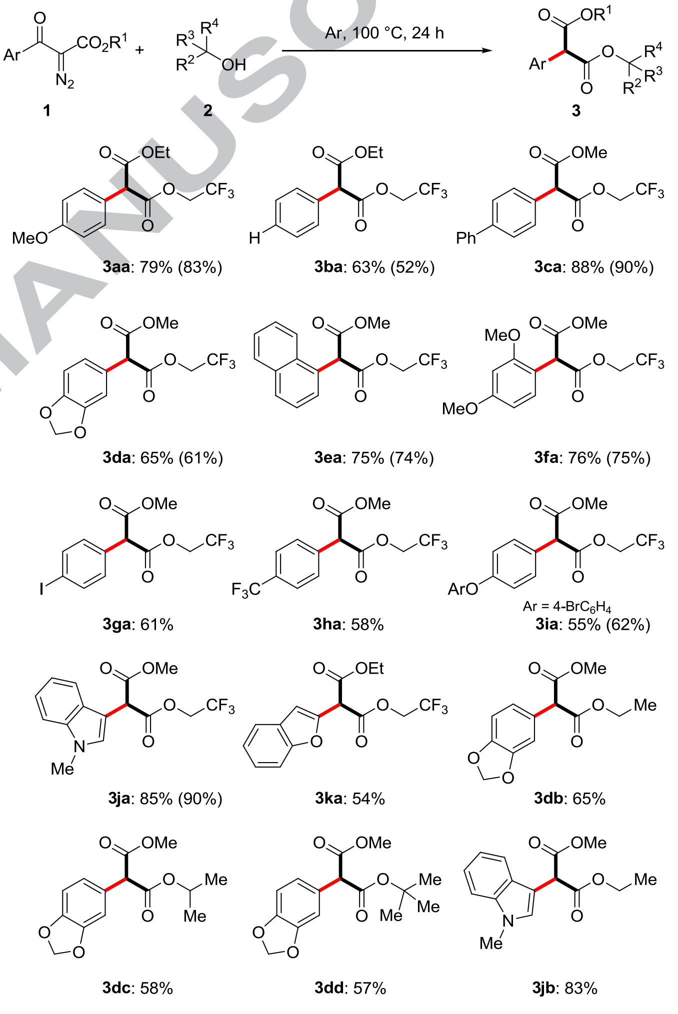
[a] Reaction conditions **A**: **1a** (0.5 mmol), TFE (**2a**, 1.0 mL), $AgSbF_6$ (10.0 mol %), Et_3N (10.0 mol %), under Ar, 100 ℃, 24 h; **B**: **1a** (0.5 mmol), TFE (**2a**, 1.0 mL), under Ar, 100 ℃, 24 h. TFE = trifluoroethanol.

[b] Isolated yield.

[c] TFE (**2a**, 2.0 equiv), toluene (1.0 mL).

[d] TFE (**2a**, 2.0 equiv), 1,4-dioxane (1.0 mL).

With the optimized reaction conditions in hand (Table 1, entry 11), we next explored the substrate scope of 2-diazo-3-aryl-3-oxopropanoates with alcohols (Scheme 1). The reaction of aryl diazo compounds **1** bearing various electron-rich or electron-deficient substituents with 2,2,2-trifluoroethanol (**2a**) provided the desired α-aryl malonates **3** under transition metal-free reaction conditions. Meanwhile, parallel reactions were also repeated under $AgSbF_6$-Et_3N catalysis, showing no significant differences on the yields (**3aa**–**fa**, **3ia**). It is worth noting that indole and benzofuran derivatives (**1j**–**k**) also proved to be viable starting materials, providing the corresponding products **3ja** and **3ka** in good yields of 90% and 54%, respectively. Besides, the 2,2,2-trifluoroethanol, other representative alcohols, such as ethanol (**2b**), iso-propanol (**2c**) and tert-butanol (**2d**), were also successfully employed in the reactions, offering the products **3db**, **3dc**, **3dd** and **3jb** in moderate to good yields, respectively.



3aa: 79% (83%) **3ba**: 63% (52%) **3ca**: 88% (90%)

3da: 65% (61%) **3ea**: 75% (74%) **3fa**: 76% (75%)

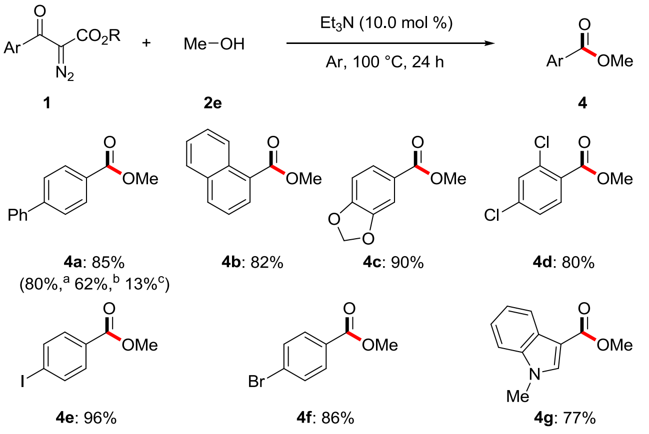
3ga: 61% **3ha**: 58% **3ia**: 55% (62%)

3ja: 85% (90%) **3ka**: 54% **3db**: 65%

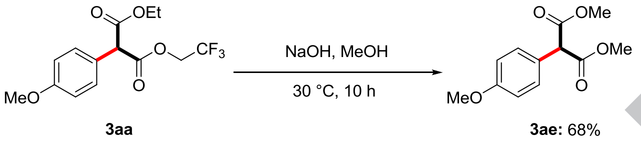
3dc: 58% **3dd**: 57% **3jb**: 83%

Scheme 1. Substrates scope: Reactions of 2-diazo-3-aryl ketoesters and alcohols. Yields within parentheses were obtained under [Ag] catalysis (reaction conditions **A**).

However, an unexpected C–O bond formation and C–C bond cleavage occurred under the standard reaction conditions, when methanol was utilized as the nucleophile and solvent. In contrast, the expected Wolff rearrangements, even the O–H insertion to the intermediacy of carbenes were not observed at all.[13a, 19] Interestingly, the formation of product **4** could be promoted by catalytic amount of Et_3N or $AgSbF_6$, while significantly decreased yield of product **4a** was obtained in the absence of base and sliver. However, the early findings were observed when sodium hydride/methoxide was used as the base.[15a, 20] Among a set of 2-diazo-3-aryl-3-oxopropanoates **1**, diversely decorated methyl benzoates were obtained in high yields (**4a**–**f**), as was also observed when using substrate **1j** with an indole (Scheme 2).



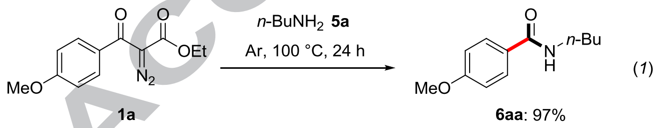
Scheme 2. Triethylamine promoted novel C–C bond cleavage with MeOH. [a] $AgSbF_6$ and Et_3N (10.0 mol %). [b] $AgSbF_6$ (10.0 mol %). [c] Without Et_3N and $AgSbF_6$.

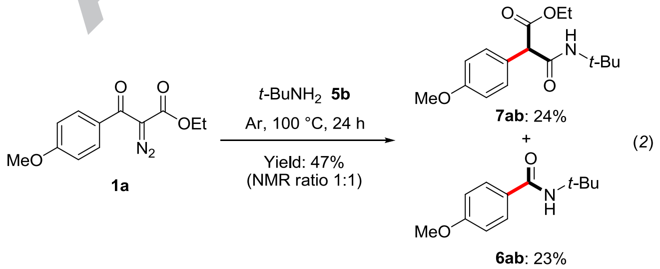


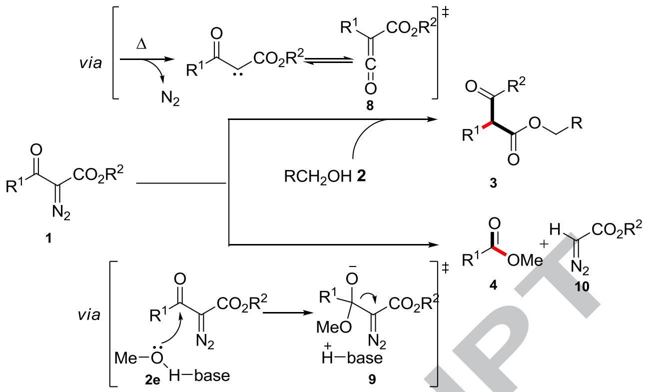
Scheme 3. Transesterification of **3aa** under alkaline conditions.

Moreover, the synthesis of α-aryl dimethyl malonate was proceeded by a facile transesterification of **3aa**, producing the desired product dimethyl 2-(4-methoxyphenyl)malonate (**3ae**) in 68% yield (Scheme 3).

Thereafter, the reactivity of alkylamines was also tested for the reaction. Benzamide **6aa** was formed as the sole product when *n*-butylamine **5a** as the nucleophile (eq. 1). However, more sterically hindered *t*-butylamine delivered the Wolff rearrangement product **7ab** and aryl amide **6ab** in similar efficacy (eq. 2).







Scheme 4. Proposed reaction mechanism.

Finally, we proposed the α-aryl malonates could result from Wolff rearrangement of the putative intermediate ketene **5**, along with subsequent addition of alcohol **2** into the product **3**.[13, 14] However, the aromatic methyl ester **4** is likely obtained through a nucleophilic addition of MeOH into 2-diazo-3-aryl-3-oxopropanoate, followed by elimination of the thus obtained intermediate **9** (Scheme 4).

In summary, we have developed a convenient and efficient methodology for the synthesis of α-aryl malonates by the thermochemical excitation of 2-diazo-3-aryl ketoesters without the use of transition-metal catalysts, which could not only make the process environmentally-benign, but also further expand the application of Wolff rearrangement in organic synthesis. However, an unusual C–C bond cleavage and C–O/(N) bond formation occurred, when methanol or alkylamine was utilized as the reaction medium, delivering aromatic ester/amide as the product.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at …

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Graphical Abstract

Thermolysis of 2-diazo-3-aryl ketoesters: new route to α-aryl malonates and aromatic esters

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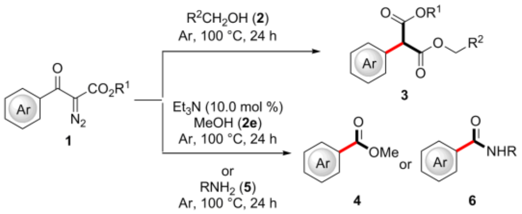
Zhao Zhang,† Mengyao Tang,† Lei Zang, Liang-Hua Zou and Jie Li*



Highlights:

1. Expedient route to α-aryl malonates.
2. Et_3N promoted C-C bond clevage, along with C-O/N bond formation.
3. Environmentally-benign fashion.